REMARKS

Reconsideration of this application, as amended, is respectfully requested. An RCE accompanies this Amendment.

Claims 8-15 and 17-23 stand rejected. In this response, no claims have been amended and no claims have been canceled. New claim 26 has been added. Applicants reserve all rights with respect to the applicability of the Doctrine of Equivalents.

Rejections- 35 U.S.C. § 102(b)

Claims 8, 9, 11, 15 and 23 stand rejected under 35 U.S.C. § 102(b) as being anticipated by U.S. Patent Publication 2002/0142413 to Brady et al. ("Brady").

Applicants respectfully submit that Brady ('413) does not teach each and every feature of independent claim 8. Independent claim 8 is directed to a method of fabrication of a scaffold comprising, *inter alia*, "leaching the scaffold in an ultrasonic bath of solvent to remove a first polymer of the at least two polymers, all other polymers of the at least two polymers being inert to the solvent, wherein leaching of the first polymer is controlled so that removal of the first polymer occurs to a greater extent at a surface of the scaffold, and to a lesser extent at a core of the scaffold." In application, the solvent may partially dissolve the first polymer while the ultrasonic vibrations remove the loose particles in the polymer blend. The depth of penetration of the effect may remove the first polymer to a greater extent at a surface of the scaffold than at a core of the scaffold. Thus, the effect of the ultrasonic leaching allows for the controlled differential leaching of the surface and core.

Brady discloses utilizing a solvent extraction process to remove leachables from a tissue-engineering scaffold. The Examiner states in the second paragraph on page 5 of the Office Action that the solvent extraction process of Brady allegedly inherently maximizes leaching of a polymer at the surface of the scaffold, resulting in greater porosity at the surface of than the core. Thus, the Examiner alleges that the solvent extraction process dissolves a polymer to create pores. Applicants respectfully disagree.

Brady does not expressly or inherently teach that the solvent extraction process increases porosity by removing a polymer. The porosity of the scaffold of Brady is not created by the solvent extraction process (called leaching by the Examiner). Rather, blowing is utilized to create the porosity. See, for example, paragraphs [0166]-[0168] where it is described that

blowing is utilized for void creation, and also paragraph [0190] where it is described that "This removal of air from the materials controls the number of very large voids throughout the material."

In contrast, the solvent extraction process with MEK referred to by the Examiner at pages 8-9, Example A of Brady has the purpose of ensuring "that no chemicals leach from the scaffold, in use." See also paragraph [0104]. It is noted that this solvent extraction process takes place after the formation of voids by the removal of air was carried out. Further, paragraph [0177] describes that "[c]onventional solvent extraction involves exposing a polymer to a solvent that has minimal effects on the polymer. Low molecular weight chemicals migrate from the near surface region into the solvent." Thus, the solvent does not dissolve a polymer and thus does not create pores. Therefore, the solvent cannot be used to create pores by removing a polymer. This is further supported in paragraphs [0178]-[0179] where it is described that the solvent has massive volume swelling on the substrate, and that the recovery process brings the scaffold back to its original geometry. That the original geometry is retained is therefore another indication that no pores are formed by use of a solvent leaching process. If the solvent in Brady would have been used to create pores by removal of a polymer it could not be said that after the use of a solvent that the "original geometry" is retained.

The Examiner additionally relies upon standard physical chemistry to support an assertion of inherency, that a solvent would require more time to diffuse to the center and have less access to the polymer being dissolved at the core than the polymer being dissolved at the surface. However, this argument does not appear to be logical in light of the teaching of Brady. For instance, from the order or manufacturing steps described in Example A it is apparent that the voids are formed (by removal of air) before solvent extraction with MEK is carried out. Thus, the solvent has no problems to access even the core of the scaffold because the solvent can easily flow through the pores already created before the scaffold is brought in contact with the solvent. This view is corroborated by the description in paragraph [0146] of Brady where it is described that "voids larger than 300 microns are not desired per this invention. However, a small number of voids in excess of 300 microns improves the ease with which fluids can migrate to and from the core of the scaffold" (emphasis added). The Table in paragraph [0144] gives an overview about the void and pore size in the scaffolds described in Brady. Thus, diffusion of a solvent per standard physical chemistry does not necessarily proceed in the manner suggested by

the Examiner in the scaffolds of Brady because the pores already exist and the solvent can freely move towards and away from the core of the scaffold.

Therefore Brady does not teach each and every feature of independent claim 8. Claims 9, 11, 15 and 23 are dependent, either directly or indirectly, thereon and are patentable for at least the same reasons as independent clam 8. Accordingly, applicants respectfully request the withdrawal of the rejections of claims 8-15 and 17-23 under 35 U.S.C. § 102(b).

Rejections- 35 U.S.C. § 103(a)

Claims 8-11, 13, 15 and 17-23 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over WO 02/060508 to Isotis N.V. ("Isotis") in view of U.S. Patent No. 6,149,688 to Brosnahan et al. ("Brosnahan") and U.S. Patent No. 6,063,894 to Phipps et al. ("Phipps"). Claims 8-15 and 17-23 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Isotis in view of Brosnahan and Phipps, as in claims 8-11, 13 and 15-23 above and further in view of U.S. Patent Publication 2004/0258732 to Shikinami ("Shikinami") and U.S. Patent No. 6,712,845 to Hossainy ("Hossainy").

Applicants respectfully submit that claim 8 is not obvious over the combination of references for several reasons. It is submitted that the references do not teach or suggest the feature of ultrasonic leaching to provide controlled differential leaching of a first polymer at the surface and core as required in independent claim 8. It is additionally submitted that a person of ordinary skill in the art at the time of applicants' invention would not have combined Isotis, Brosnahan and Phipps as suggested by the Examiner. Indeed Isotis teaches away from the proposed combination of references, supporting the conclusion that the proposed combination of references can only be the result of impermissible hindsight reasoning based upon applicants' own disclosure.

Isotis ('508) discloses mixing two polymers and removing one of the polymers by immersing in a solvent. In particular, see page 2, lines 21-24 where it is stated that "[i]t is a goal of the present invention to provide for porous bodies that have a reproducible and well-defined pore size and porosity. It is a further goal to come to porous bodies with interconnected pores, preferably homogenously distributed throughout the porous body." In order to obtain a

homogenous distribution of well-defined pores, Isotis teaches at page 9, lines 20-26 to repeat an immersion step in UV treated demineralized water. The experimental section of Isotis further supports the view that a homogeneous distribution of well-defined pores is the goal of Isotis. For example, it is described in Example 1 at page 11, lines 8-9 that the "[r]esults showed that 90% of the pores could be reached by interpore connections with a diameter of 100 μm or higher ... No cracks, inhomogeneity and black spots were determined" (emphasis added). Similar comments can be found in Example 2 (page 12, lines 12-15) and Example 3 (page 13, lines 1-3).

Accordingly, Isotis discloses the importance of achieving a structure with a homogenous distribution of interconnected pores, and does not disclose or suggest ultrasonic leaching or controlled differential leaching of a first polymer at the surface and core. Indeed Isotis teaches away from controlled differential leaching of a first polymer at the surface and core.

On page 9 of the Office Action the Examiner points to page 9, lines 21-23 of Isotis where it is stated "Generally, it will be desired to repeat this procedure in demineralized water to achieve a substantially complete removal of the soluble particles" and appears to suggest that this portion of the Isotis teaches producing a structure which does not have a homogenously distributed and interconnected pores throughout the porous body. Applicants disagree.

When interpreting the disclosure of a prior art reference it must be considered in its entirety, including portions that would lead away from the claimed invention. *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983), cert. denied, 469 U.S. 851 (1984). See also MPEP 2141.02. When considering the entirety of a prior art reference "it is impermissible within the framework of section 103 to pick and choose from any one reference only so much of it as will support a given position, to the exclusion of other parts necessary to the full appreciation of what such reference fairly suggests to one of ordinary skill in the art." *Bausch & Lomb, Inc. v. Barnes-Hind/Hydrocurve, Inc.*, 796 F.2d 443, 230 USPQ 416 (Fed. Cir. 1986), cert. denied, 484 U.S. 823 (1987).

With all due respect, it submitted that contrary to the Examiner's interpretation of page 9, lines 21-23, one of ordinary skill in the art would understand that when considered with the whole of Isotis that page 9, lines 21-23 is describing a preferred method which can be used to achieve substantially complete removal of the soluble particles, and that page 9, lines 21-23 is not merely describing that achieving substantially complete removal of the soluble particles is a

preferred embodiment. Specifically, the preferred method includes repeating of a submersion step in demineralized water, which is more preferably UV treated. See also Example 1 (page 10, line 27 – page 11, line 3) where the preferred method of repeating submersion in demineralized water was repeated (refreshed) at least 4 times every 4-16 hours until the conductivity of the demineralized water was below 25 μS for a more than 4 hours.

It is respectfully submitted that when considered in its entirety, one of ordinary skill in the art would understand that Isotis consistently discloses achieving a homogeneous distribution of well-defined pores, and that Isotis leads away from controlled differential leaching of a first polymer at the surface and core. Such an interpretation is consistent throughout the disclosure, and is not limited to a preferred embodiment. For example, page 2, lines 21-24; page 9, lines 20-26; page 11, lines 8-9; Example 1 (page 10, line 27 – page 11, line 11); Example 2 (page 12, lines 12-15) and Example 3 (page 13, lines 1-3).

The Examiner additionally alleges in the last full paragraph on page 6 of the Office Action that "wherein leaching of the first polymer is controlled so that removal of the first polymer occurs to a greater extent at a surface of the scaffold, and to a lesser extent at a core of the scaffold" is inherent in Isotis per standard physical chemistry. Applicants respectfully disagree.

"In relying upon the theory of inherency, the examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art." *Ex parte Levy*, 17 USPQ2d 1461, 1464 (Bd. Pat. App. & Inter. 1990) (emphasis in original).

All inventions which are made rely on mechanisms which either naturally occur in nature or are initiated by men. The subject matter of independent claim 8 is directed toward controlled leaching in an ultrasonic bath to remove the first polymer to a greater extent at a surface than at a core of the scaffold. It is respectfully submitted that the Examiner has failed to describe why Isotis necessarily discloses "wherein leaching of the first polymer is controlled so that removal of the first polymer occurs to a greater extent at a surface of the scaffold, and to a lesser extent at a core of the scaffold". As described in detail above, the "goal" of Isotis referred to therein as well as the description of the method used do not allow concluding that anything else but the manufacture of a scaffold with a homogeneously distributed and well-defined pore size is to be

obtained. Accordingly, it is not clear how Isotis can necessarily describe "wherein leaching of the first polymer is controlled so that removal of the first polymer occurs to a greater extent at a surface of the scaffold, and to a lesser extent at a core of the scaffold" when the "goal" of Isotis referred to therein as well as the description of the method used do not allow concluding that anything else but the manufacture of a scaffold with homogenously distributed and well-defined pore size is to be obtained.

Therefore, it is respectfully submitted that Isotis does not expressly, implicitly, or inherently teach or suggest the feature of controlled differential leaching of a first polymer at the surface and core as required in independent claim 8. Indeed Isotis teaches away from controlled differential leaching of a first polymer at the surface and core. Furthermore, Isotis does not teach or suggest ultrasonic leaching to provide controlled differential leaching of a first polymer at the surface and core as required in independent claim 8.

The Examiner suggests on pages 7 and 8 that it would have been obvious to modify Isotis in view of Brosnahan ('688) to "provide a porosity gradient as taught in the '688 patent" and that one of ordinary skill in the art would have been motivated to do so because Isotis teaches at page 3, lines 19-24 "varying the amount and/or dimensions of either the polymer powder or the soluble particles, the pore-size, porosity, and/or amount of interconnected pores can be controlled in a manner that has not been previously disclosed. Applicants disagree with the proposed motivation in at least two material respects.

Firstly, it is respectfully submitted that the paragraph at page 3, lines 19-24 does not disclose what the Examiner purports. Rather, this paragraph merely teaches that the initial amount and dimensions of polymer powder and soluble particles used, respectfully, can be initially controlled during blending to ultimately affect pore size and distribution. Isotis does not describe controlling leaching after blending "so that removal of the first polymer occurs to a greater extent at a surface of the scaffold, and to a lesser extent at a core of the scaffold" as required in independent claim 8. Thus, it is submitted that one of ordinary skill in the art would not have found motivation to for the proposed modification in Isotis.

Secondly, while Brosnahan describes an artificial bone graft implant with a porosity gradient at column 4, lines 52-56, the porosity gradient is not created by controlled leaching. Rather, it is only mentioned at column 4, lines 49-50 that a different porosity of the core and

shell is obtained by burning out during sintering. Indeed, Brosnahan fails to disclose any teaching on how the pore gradient at column 4, lines 52-56 is manufactured. Accordingly, it is not apparent how the mention of a process of burning out binder during sintering can provide any further insight in how to control leaching of the first polymer "so that removal of the first polymer occurs to a greater extent at a surface of the scaffold, and to a lesser extent at a core of the scaffold" as required in independent claim 8. Thus, it is submitted that one of ordinary skill in the art would not have found motivation to for the proposed modification in Brosnahan.

Therefore, it is respectfully submitted that neither Isotis nor Brosnahan teach or suggest the controlled leaching method of independent claim 8. Furthermore, it is respectfully submitted that one of ordinary skill in the art would not have been motivated to modify the process of Isotis in view of Brosnahan to produce the porosity gradient disclosed in Brosnahan. As described above, Isotis teaches away from an inhomogenous porosity. Brosnahan describes creating porosity by sintering rather than leaching. Neither reference provides guidance to one of ordinary skill in the art as to how to modify the method of Isotis to obtain the process taught and claimed in independent claim 8. As a result, it is respectfully submitted that one of ordinary skill in the art would not have been motivated to modify the process of Isotis in view of Brosnahan, and that the proposed combination of references can only be the result of impermissible hindsight reasoning based upon applicants' own disclosure.

The Examiner suggests on pages 7 and 8 that it would have been obvious to modify Isotis in view of Brosnahan ('688) and further in view of Phipps ('894) "because the '894 patent teaches the enhancement of mechanical properties of the polymer by leaching compounds in an ultrasonic bath ('894, column 4, lines 19-27). Phipps discloses a process of ultrasonic purification of polymers in which any impurities remaining from the polymerization process are removed from the polymer. "Generally, leaching is conducted until greater than about 99% of leachant is removed." Col. 8, lines 3-4. Thus, Phipps discloses a process for complete removal of a leachant, and does not disclose or suggest ultrasonic leaching to provide controlled differential leaching of a first polymer at the surface and core. Accordingly, Phipps does not teach or suggest the controlled leaching method of independent claim 8, nor does Phipps provide any guidance to one of ordinary skill in the art as to how to modify the method of Isotis to obtain the process taught and claimed in independent claim 8.

Therefore, it is respectfully submitted that Isotis, Brosnahan and Phipps, alone or in combination, do not teach or suggest the controlled leaching method of independent claim 8. It is additionally submitted that one of ordinary skill in the art would not have been motivated to modify the process of Isotis in view of Brosnahan and Phipps, and that the proposed combination of references can only be the result of impermissible hindsight reasoning based upon applicants' own disclosure.

The Examiner relies upon Shikinami ('732) as disclosing compression moulding. The Examiner relies upon Hossiany ('845) as disclosing specific solvents. Applicants respectfully submit that Shikinami and Hossiany do not remedy the deficiencies of Isotis, Brosnahan and Phipps as discussed above.

Therefore, applicants respectfully submit that independent claim 8 is not rendered obvious over the cited references. Claims 9-15 and 17-23 are dependent, either directly or indirectly, thereon and are patentable for at least the same reasons as independent clam 8. Accordingly, applicants respectfully request the withdrawal of the rejections of claims 8-15 and 17-23 under 35 U.S.C. § 103(a).

New Claim

New claim 26 requires, *inter alia*, "the scaffold is exposed to the ultrasonic bath of solvent for 5 minutes to 120 minutes such that the first polymer is only partially leached or not leached at all at the core." It is applicants' understanding these features are not taught by the prior art of record.

It is respectfully submitted that in view of the amendments and arguments set forth herein, the applicable rejections have been overcome. The Examiner is invited to contact applicants' representative Jacob T. Aikin at (408) 720-8300 if the Examiner believes such action would expedite examination of the present application.

If there are any additional charges, please charge Deposit Account No. 02-2666.

Respectfully submitted,

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